BENZOIMIDAZOLE DERIVATIVES AS ANTICANCER AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a National Phase Entry of International Patent Application No. PCT/EP2017/073801, filed on Sep. 20, 2017, which claims priority to European Patent Application Serial No. 16306203.7, filed on Sep. 20, 2016, both of which are incorporated by reference herein.

BACKGROUND AND SUMMARY

[0002] The technical domain of the invention is anticancer drugs.

[0003] Chemotherapy, together with surgery and radiotherapy, remains one of the most used approaches for the treatment of cancer. Although some tens of anticancer compounds have been approved for clinical use, there is still a constant need for more selective, more effective and less toxic novel therapeutics. Thus there is an ongoing need in the art to optimize anticancer drugs.

[0004] In this context, the invention relates to benzoimidazole derivatives having anticancer properties. The compounds according to the invention are able to firstly inhibit the protein/protein interactions of the MAP Kinase Erk, leading to inhibition of proliferation, and secondly to induce apoptosis of cancer cells, notably as demonstrated in human cancer cell lines of lung, colon, melanoma, sarcoma and pancreatic cancer cell lines, but not of normal cells. The compounds according to the invention are able to inhibit Erk1/2 interaction with MyD88, Erk meaning Extra cellular signal-regulated kinase and MyD88 meaning Myeloid Differentiation primary response gene 88.

[0005] Advantageously, the compounds of the invention are also able to stimulate the immunogenic cell death (ICD) via the display of markers like the immunogenic cell death markers. Secretion of ATP, an active process that occurs during ICD, was also induced by the compounds of the invention on the cell membrane notably of mouse lung cells and human colon cells in particular, and of mouse tumor cells. Advantageously, the cell death induced by the compounds of the invention is generally accompanied by the exposure of calreticulin (CRT) on the cell membrane notably of mouse lung cells and human colon cells, and of mouse tumor cells. Indeed, the presence of CRT on the apoptotic cell surface provides an "eat me" signal to macrophages and dendritic cells, leading to the activation of the immune system. Advantageously, the compounds of the invention are able to induce apoptosis by a mechanism distinct from that of kinase inhibitors.

[0006] The present invention intends to provide new compounds having one or more of the following characteristics:

[0007] the compounds of the invention are not kinase inhibitors which are known to generally affect multiple molecular targets generating many side effects;

[0008] the compounds of the invention are surprisingly inducers of the immune system;

[0009] the compounds of the invention are safe in vivo at efficient doses;

[0010] the compounds of the invention are less toxic compared to conventional chemotherapy generating less side effects.

[0011] One of the purpose of the invention is to provide compounds of formula (I) or (I') as described below, notably for use as a medicament in cancer treatment, as well as the pharmaceutically acceptable salts thereof, stereoisomers or mixtures of stereoisomers thereof, in any proportions, particularly a mixture of enantiomers, and especially a racemic mixture. Another purpose of the invention is to provide a pharmaceutical composition comprising at least one compound of formula (I), (I'), (II) or (III) and a pharmaceutically acceptable carrier. Another purpose of the invention is to provide a method for inhibiting oncogenesis and/or cancer cell growing through the MyD88/ERK cell pathway, in particular for inhibiting the MyD88/ERK interaction, and/or for stimulating the display of immunogenic cell death (ICD) markers on the cell membrane of cancer cells comprising the administration to a person in need thereof of an effective amount of a compound of formula (A) as described below, or a pharmaceutically acceptable salt thereof, a stereoisomer or mixture of stereoisomers thereof, in any proportions, particularly a mixture of enantiomers, and especially a racemic mixture.

Definitions

[0012] The term "halogen" or "halo", as used in the present invention, refers to a fluorine, chlorine, bromine or iodine atom.

[0013] The term "amino group", as used in the present invention, refers to a group NH_3, NH_2Alk1 or $NAlk1Alk2$ in which Alk1 and Alk2, identical or different, represent a (C1-C6)-alkyl group as defined below. For example, it can be a dimethylamino group.

[0014] The term "(C1-C6)alkyl", as used in the present invention, refers to a straight or branched monovalent saturated hydrocarbon chain containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, and the like.

[0015] The term "(C1-C6)alkylcarbonyl", as used in the present invention, refers to a (C1-C6)alkyl group as defined above bound to the molecule via a —C(═O)— group, including, but not limited to acetyl, propionyl, n-butyryl, sec-butyryl, t-butyryl or iso-propionyl.

[0016] The term "oxy(C1-C6)alkylcarbonyl", as used in the present invention, refers to a (C1-C6)alkylcarbonyl group as defined above substituted by at least one oxygen atom, and bound to the molecule via a —C(═O)— group.

[0017] The term "(C1-C6)haloalkyl", as used in the present invention, refers to a (C1-C6)alkyl group as defined above substituted by at least one halogen atom, and preferably by at least one chlorine or fluorine atom. It can be in particular a trifluoromethyl group.

[0018] The terms "(C1-C6)alkanoic acid amide" as used in the present invention, refers to a (C1-C6)alkyl group as defined above bound to a —C(═O)— group, the carbon of the CO group is bound to a nitrogen atom (NH), the (C1-C6)alkanoic acid amide is bound to the molecule via the alkyl group.

[0019] The term "(C1-C6)alkoxy", as used in the present invention, refers to a (C1-C6)alkyl group as defined above bound to the molecule via an oxygen atom, including, but not limited to, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy, n-pentoxy, n-hexoxy, and the like.